EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 3
296-301
Year: 2023

TO DETERMINE THE EFFECT OF DIFFERENT PENETRATION ENHANCERS ON RELEASE OF CAFFEINE FROM GEL FORMULATION

Mohit Kumar*[1], Dr. Shailesh Kumar Ghatuary[2], Mamta Dubey[3] and Sarika Chaturvedi[3]

Undergraduate Student[1], Principal[2] and Assistant Professor[3]
Shri RLT Institue of Pharmaceutical Science and Technology, Ekdil (206126) Etawah, Uttar Pradesh, India.

***Corresponding Author: Mohit Kumar**
Undergraduate Student, Shri RLT Institue of Pharmaceutical Science and Technology, Ekdil (206126) Etawah, Uttar Pradesh, India.

Article Received on 16/01/2023 **Article Revised on 06/02/2023** **Article Accepted on 26/02/2023**

ABSTRACT
The aim of present study is to determine the effect of different penetration enhancers on release of caffeine from gel formation this research was carried out by pre-formulation studies such as, physical appearance, UV and melting point determination. The optimized formulation was characterized by parameters like drug content, spread ability of gel, pH, ex-vivo and drug diffusion study. Ex -vivo study on the pig ear skin model and accelerated stability studies were done. Melting point of caffeine was found to be within the range i.e., 235-238°C. The UV maxima were found to be 273nm. The pH of caffeine gel formulations was found in the range of 5.34 to 6.19. Caffeine gel was prepared using different penetration enhancers like Ethanol, Glycerin, PEG-400 and PEG-200. The best gel was selected on the bases of drug permeation results. The formulation having Ethanol as penetration enhancer was found to be best formulation as it gives maximum skin, permeation results.

KEYWORDS: Penetration enhancer, caffeine gel, UV spectroscopy, skin permeation, Transdermal drug delivery.

1. INTRODUCTION
Transdermal delivery system of drugs is a novel drug delivery system. This system breaks many barriers in drug therapy like need of assistance and uncomfortable administration. Transdermal delivery has many advantages over conventional modes of drug administration like it potentially decreases side effects, avoids hepatic first pass metabolism and improves patient compliance (Allen et al., 2005 and Barry, 2002) Gels are semisolid systems in which a liquid phase is constrained within a three-dimensional polymeric matrix (consisting of natural or synthetic gums) in which a high degree of physical (or sometimes chemical) cross-linking has been introduced. The clarity range from clear to a whitish translucent. The polymers are used between 0.5-15 % and in most of the cases they are usually at the concentration between 0.5-2%. Gels are usually clear transparent semisolid containing the solubilised active substances (Chandira et al., 2010). However, the skin, especially the stratum corneum provides resistance for drug absorption and it is the rate limiting step in percutaneous absorption. The permeation of drugs through the stratum corneum can be enhanced by physical methods and chemical modification or by the use of chemical penetration enhancers. Chemical penetration enhancers modify the barrier properties of the stratum corneum and hence increase the drug permeability across the skin. Chemical enhancer should be non-toxic, nonallergenic and also (Michniak et al., 1993).

2. MATERIALS AND METHODS
Table 1: List of active drug, excipients, solvent and chemical.

Sr.No.	Materials	Manufacture, Location
1.	Caffeine	Qualikems Fine Chem. Pvt. Ltd., India
2.	Carbopol940	SRL lab, India
3.	Triethanolamine	Loba Hemie Pvt.Ltd.,India
4.	Ethanol	Qualikems Fine Chem.Pvt.Ltd.,India

2.1 Pre-formulation Studies
A pre-formulation study was done during the development of formulation by detecting its physicochemical properties. Laboratory studies to determine the characteristics of active substance and excipients that may influence formulation and process design and performance knowing about the physicochemical properties and biopharmaceutical

properties will help to decide the formulation which was beneficial in term to drug delivery. It will increase the chances of public safety and improve quality of product. So, in this project were evaluating the drug by following pre-formulation test.

2.2 Description

Physical evaluation revealed that the caffeine is an off-white powder.

2.3 Detection of Melting Point

Melting point detection done by capillary tube is very simple and laboratory scale method. So, detection of caffeine was done by capillary tube method. In this method capillary was ignited from the bottom and sealed it. After that a small pinch of drug was added through a light tapping. Standard operating procedure was followed during the use of the melting point apparatus. Before inserted the capillary tube temperature was maintained 30°C below the expected melting point. After that capillary was kept into the small hole present into the apparatus and one big hole used for inserted the thermometer. Temperature was detected when drug started to melt.

2.4 UV Spectrophotometric Method Development

Analytical method development gives the analysis method to sure the accuracy of the instruments (Manasa *etal*., 2014). Results shows that an accurate and specific method which has been developed. Basically, it is the documented evidence that the system works properly or not. Validation shows that the analytical procedure is satisfactory for purpose which are consider to performing. A UV spectrophotometer method can use this principle to quantify the analytes in a sample based on their absorption characteristics. UV–visible is used to determine the size and concentration of NPs. UV spectrum was identified by dissolving the drug into the water and by serial dilution to make the solution of 10µg/ml. Solution than was added to the cuvette and scanned into the range 200-400nmin UVspectrophotometer. Sample showed the highest absorption at 272.5nm. Therefore, all other validation tests were performed at 272.5nm.

2.5 Preparation of Standard Curve

Standard stock solution of caffeine was prepared by dissolving 50 mg pure drug in 50 ml standard volumetric flask with water followed by sonication for 5 min. The obtained solution of 1 mg/ml was further diluted to prepare six standard concentrations namely 2, 4,6, 8, 10, 15, 20 µ/ml.

Each standard concentration was run in triplicates and the average value was used for the preparation of standard curve by plotting concentration speak area. Standard curve was Constructed with peak area (Y-axis) against concentration (X-axis) followed by estimation of coefficient of correlation using Microsoft excel. The amount of caffeine present in the tested samples were calculated through the standard curve.

2.6 Preparation of Caffeine Gel

The gel prepared by dissolving 2% of caffeine in a minimum volume of deionized water. In another beaker, 1.5% Carbopol dissolved in distilled water. The Carbopol solution was then put in the solution of caffeine. Then dilute triethanolamine solution (20% v/v) was added drop wise to produce clear, transparent and desired consistency gel, and then ethanol 5%usedas penetration enhancer.

2.7 Characterization of Gel

2.7.1 Drug Content Study

An amount of 1gm of gel was accurately weighed and dissolved in 50mL of distilled water. After suitable dilution the drug content was analyzed by using developed UV method (Al-Bazzazand Al-Kotaji, 2018).

2.7.2 Determination of Gel pH

The pH of gel was measured using digital pH meter.

2.7.3 Spread ability Study

Spreadability of gel was determined by using two glass slides which are equal in shape (square) and size. 2gm of gel was placed on one glass slide and area covered by gel was marked (initial diameter). Then the second slide was placed on first and some weight was placed in that slide. Area covered by gel was marked (finaldiameter) and spreadability was calculated by given formula:

Spreadability = Finaldiameter- Initial diameter/ Initial diameter*100

2.7.4 *Ex-Vivo* Skin Permeation Study

Ex-vivo drug release and permeation of the drug would be measured using modified Franz diffusion cell with pig ear skin as barrier medium (Al-Bazzaz and Al-Kotaji, 2018). The temperature of the receptor medium was maintained at 37±1ºC. The receptor compartment was contained 13.3 ml distilled water and constantly stirred by magnetic stirrer at 350 RPM. Skin samples were fixed over the diffusion cells in such a way that the dermis faced the receptor compartment while stratum corneum side faced the donor compartment. An amount of 1gm gel formulation was administered in the donor compartment. 0.3 ml samples were withdrawn through sample port of the diffusion cells at 30, 60, 90, 120, 180, 240 and 360 minutes and analyzed by UV method. To maintain a sink condition throughout the study period, the receptor phase, once sampled, was immediately replenished with equal volume of dissolution medium. Once the permeation study is completed, the skin attached with diffusion cell was removed to determine the amount of drug deposited in the skin layer. Skin samples were thoroughly washed with distilled water, cleaned with cotton wetted in normal saline solution. The skin was homogenized with 10 ml of water to extract the drug retained in the skin. The suspension thus obtained was filtered with a 0.22-mm membrane filter. The processed sample, after suitable dilution, was analyzed

by UV method.

3. RESULTS AND DISCUSSION

3.1 Pre-formulation Studies

Fig. 4: Franz Diffusion Cell.

3.2 Description

Caffeine was received from Qualikems Fine Chem. Pvt. Ltd., India. Physical evaluation revealed that the caffeine is an off-white crystalline powder. The physical appearance of formulated gel revealed that the gel is clear and transparent.

3.3 Melting point Determination

The melting point was detected by capillary melting point apparatus and it was 235.3^{0}C(table.3). It was almost same to that of reported melting point i.e., 235-238^{0}C (BritishPharmacopeia, 2009).

Table 2: Melting point determination of caffeine.

	Observed Melting Point			Reported Melting Point
MP1	**MP2**	**MP3**	**MEAN**	**235^{0}C-238^{0}C**
236^{0}C	234^{0}C	236^{0}C	235.3^{0}C	

3.4 UV Spectrophotometric Method Development

Analytical method development gives the analysis method to sure the accuracy of the instruments. Results shows that who accurate and specific method which is developed. Basically, it is the documented evidence that the system works properly or not. Validation shows that the analytical procedure is satisfactory for purpose which are consider to performing. Analytical sample of concentration (10µg/mL) shows maximum peak at 272.5 nm.273 nm was chosen as λ max due to its higher absorbance value. The main spectrum of caffeine is shown in Fig. 6.

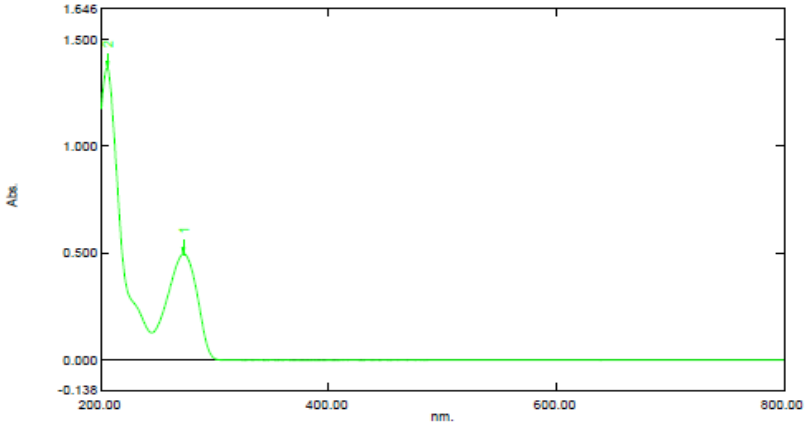

Fig. 6: The UV Spectrum of Caffeine.

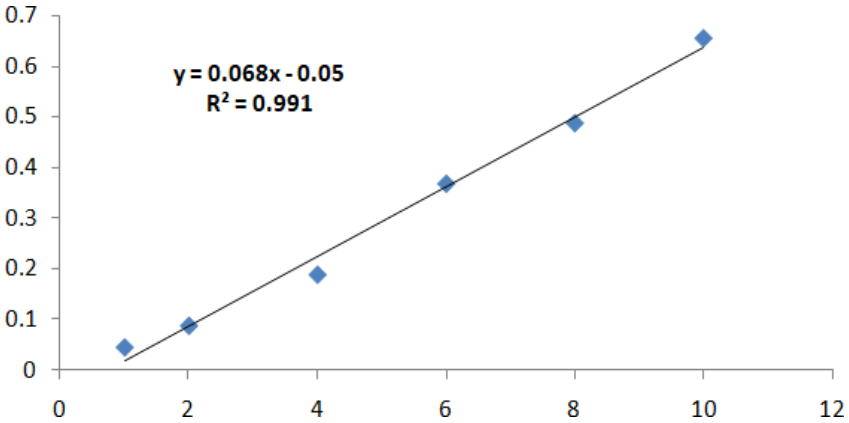

Fig.7: Calibration curve of Caffeine using UV spectrophotometer.

3.5 Characterization of Gel

3.5.1 Drug Content

The drug content was found in the range of 98.5%.

3.5.2 pH of Prepared Gel

The pH of caffeine gel formulations was found in the range of 5.34 to 6.19.

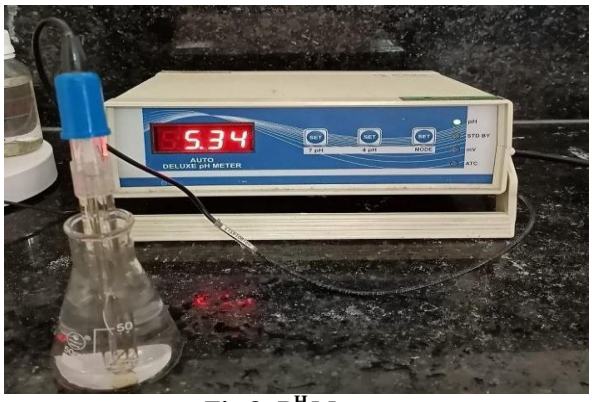

Fig.8: P^{H} Meter.

3.6 Spreadability

The spreading of gel is responsible for the uniform application of gel formulation on skin; hence the prepared gel formulation must have appropriate spreadability and that must satisfy all the ideal qualities of topical application. Spreadability was calculated using the spreadability apparatus made of wooden board with scale and two glass slides having two pans on both sides mounted on a pulley. Spreadability is the wide distribution andcirculation of information on media platforms. Spreadability of caffeine gel was found maximum with Ethanol-240%, Glycerin-220%, PEG200-180% and PEG400-200%.

Table 3: Spreadability results of caffeinegel.

Sr.No.	Formulation	Spreadability
1.	Gel with Ethano l1%	240%
2.	Gel with Glycerin 1%	220%
3.	Gel with PEG-2001%	180%
4.	Gel with PEG-4001%	200%

3.7 Results of *Ex-Vivo* Permeation Studies

Ex-vivo permeation studies were conducted as per the method described in material & methods section. Total of permeation and deposition was considered as total amount of drug permeated against 1gm gel containing 10 mg caffeine. The following section contains the result of permeation studies of individual formulation containing different percent of chemical permeation enhancers by using different methods.

Table 4: Penetration enhancement with help of different penetration enhancers.

Sr.No.	Chemical Name	Penetration
1.	Ethanol	21.93
2.	PEG-200	18.1
3.	PEG-200	17.27
4.	Propylene Glycol	14.69

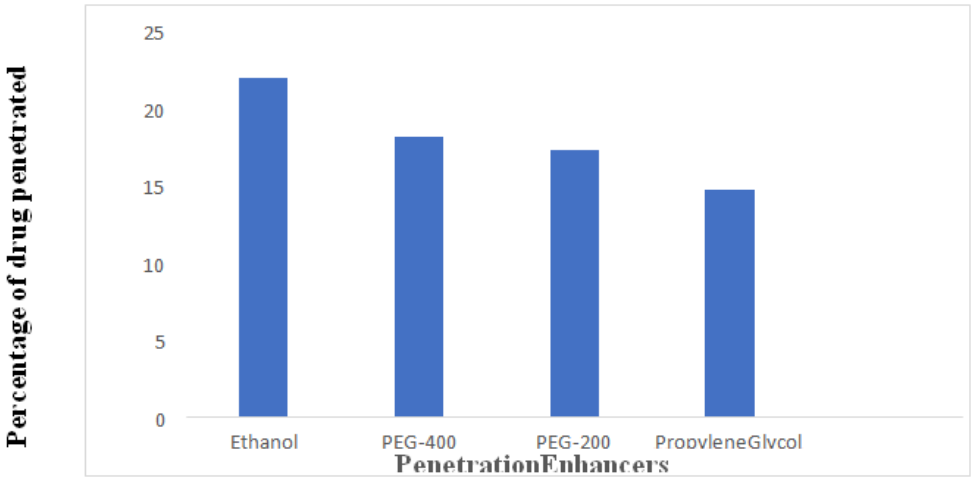

Fig. 9: Permeation enhancement with help of different penetration enhancers.

4. CONCLUSION

In this study the different penetration enhancers such as Ethanol, Glycerin, PEG 400, PEG 200 was tested for their penetration ability in varying concentration. The *ex-vivo* skin permeation of caffeine gel formulations and saturated solution of caffeine with penetration enhancer were determined. The present work deals with development of caffeine-based gel formulation design to be used topically. The following conclusions were drawn based on the experimental works performed and the data generated:

Detection of drug molecules i.e., caffeine was done by UV spectroscopy which confirmed that the caffeine was pure and free from any impurity.

Melting point was found to be 235-238°C. The UV method was developed by using the represented sample (10µg/ml.) which showed the highest absorbance at 273 nm.

The linear regression equation was found to be y-0.068x-0.05 and the coefficient of regression value was found to be R^2- 0.991. The gel formulation was further characterized for pH, spread ability, drug contented*-vivo* drug diffusion study and *in vivo* studies. The pH of caffeine gel formulations was found in the range of 5.34 to 6.19. Spreadability of caffeine gel was found maximum with Ethanol-240%.

In this study we concluded that, among all the penetration enhancers Ethanol showed maximum *ex-vivo* skin permeation for gel among all the chemical enhancers used here.

5. REFERENCES

1. Allen LV et al, (2005). Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th Edition, Lippincott Williams &Wilkins, pp. 298-315.
2. Michiniak et al ,1993 In vitro evaluation of a series of A zone analogs as dermal penetration enhancers
3. Al-Bazzaz, F.Y. and Al-Kotaji, M.(2018) Ophthalmic in-situ sustained gel of ciprofloxacin,

preparation andevaluation study, Int JApp Pharm,10(4): 153-161.
4. Manasa, S. et al. (2014) 'Method development and validation of dapagliflozin in API by RP-HPLC and UV-spectroscopy', International Journal of Pharmaceutical Science and Drug Research, 6(3): 250–252.
5. Barry B. (2002). Transdermal Drug Delivery. In Ed: Aulton M E, Pharmaceutics: The Science of Dosage Form Design, Churchill Livingston. pp :499-533
6. Chandira et al, Formulation and evaluation of herbal tablets containing ipomoea digitata linn. Extract, International Journal of Pharmaceutical Sciences Review and Research Volume 3, Issue 1, July – August 2010; page no 101 -110
7. Barry, B.W. and Williams, A.C.(1993) Terpenes as skin penetration enhancers, Drugs and the pharmaceutical sciences, 59: 95-111.
8. Chander Jhawat, V. et al. (2013) Transdermal drug delivery systems: Approaches and advancements in drug absorption through skin', International Journal of Pharmaceutical Sciences Review and Research, 20(1): 47-56.
9. Michaels A.S. et al, (1975) 'Drug permeation through human skin: the in vitro experimental measurement', AI ChE journal, 21(5): 985–996.
10. British pharmacopoeia, 2009.